Decision Memo for Screening Immunoassay Fecal-Occult Blood Test (CAG-00180N)

Decision Summary

CMS concludes that there is adequate evidence to determine that the immunoassay fecal occult blood test (iFOBT) is an appropriate and effective colorectal cancer screening fecal occult blood test for Medicare beneficiaries aged 50 years and older. The test appears to have modestly better test performance characteristics and patient compliance compared to existing methods for detecting fecal occult blood. Therefore, CMS intends to issue a positive coverage determination.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction, program memorandum, CMS ruling or Federal Register Notice, giving specific directions to our claims processing contractors. That issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare National Coverage Determinations Manual. Policy changes become effective as of the date listed in the transmittal that announces the National Coverage Determinations Manual revision.

To: Administrative File CAG: # 00180N
Screening Immunoassay Fecal Occult Blood Test

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Subject: National Coverage Determination (NCD) on Screening Immunoassay Fecal Occult Blood Test
Date: November 4, 2003

I. Decision

CMS concludes that there is adequate evidence to determine that the immunoassay fecal occult blood test (iFOBT) is an appropriate and effective colorectal cancer screening fecal occult blood test for Medicare beneficiaries aged 50 years and older. The test appears to have modestly better test performance characteristics and patient compliance compared to existing methods for detecting fecal occult blood. Therefore, CMS intends to issue a positive coverage determination.

II. Background

Colorectal cancer (CRC) is the fourth most common form of cancer and the second leading cause of cancer deaths in the United States.[1] In 2001, "an estimated 135,400 cases were diagnosed and an estimated 56,700 deaths occurred in the United States."[2] Since risks increase with age, many of these new cases and deaths occur in the Medicare population. However, many such cases and deaths are preventable. Most CRCs develop from precursor polyps; thus primary prevention is actually possible with immediate removal of precancerous polyps. Secondary prevention (early detection of a cancerous lesion) by various methods and early treatments are also essential and have been shown to improve CRC mortality.[3]

Since both precancerous and cancerous polyps may bleed, one recommended method of CRC screening is to test for occult blood in the stool annually.[4] It is important to note that regular screening every year with fecal occult blood tests (FOBTs) is necessary because bleeding may be missed with one time testing and annual screening has been shown to significantly reduce mortality.[5]

Other CRC screening tests include sigmoidoscopy, colonoscopy and barium enema; however, in this NCD, we will only address CRC screening with FOBTs. These tests are generally divided into two types: immunoassay types and guaiac types. Immunoassay (or immunochemical) fecal occult blood tests (iFOBT) use "antibodies directed against human globin epitopes."[6] Examples of iFOBTs include HemeSelect® (Beckman Coulter, Inc.), FlexSure® (SmithKline Diagnostics, Inc.), !nSure™ (Enterix, Inc.), and Instant-View™ (Alfa Scientific Designs, Inc.). While most iFOBTs use spatulas to collect stool samples, !nSure™ uses a brush to collect toilet water surrounding the stool. Most iFOBTs require laboratory processing.

Guaiac fecal occult blood tests (gFOBT) use a peroxidase reaction to indicate presence of the heme portion of hemoglobin. "Guaiac turns blue after oxidation by oxidants or peroxidases in the presence of an oxygen donor such as hydrogen peroxide."[7] Examples of gFOBTs included Hemoccult® (SmithKline Diagnostics, Inc.), Hemoccult II® (SmithKline Diagnostics, Inc.), and Hemoccult SENSA® (Beckman Coulter, Inc.). Most gFOBTs use sticks to collect stool samples and may be developed in a physician's office or a laboratory. In the past, dehydration of the sample was a concern if the test was not properly stored and tested within the specified time and rehydration of the sample with a drop of deionized water was occasionally done. However, rehydration is not currently recommended by the manufacturer for either Hemoccult II® or Hemoccult SENSA®.[8]

In 1998, Medicare began reimbursement for guaiac FOBTs, but not immunoassay type tests for CRC screening. In March 2003, CMS began consideration of a formal request from Enterix, Inc. for a national coverage determination of !nSure™ iFOBT as an annual CRC screening test. Since the fundamental process is similar for other iFOBTs, CMS used this NCD to evaluate CRC screening using immunoassay FOBTs in general.

III. History of Medicare Coverage

Medicare is a defined benefit program. An item or service must fall within a benefit category under part A or part B as a prerequisite to Medicare coverage under the fee-for-service program. § 1812 (Scope of Benefits-Part A); § 1832 (Scope of Benefits-Part B); § 1861(s) (Definition of Medical and Other Health Services). Congress has specifically authorized coverage of certain screening tests under part B of the Medicare program and has consistently made necessary conforming changes in order to ensure that payments are made. Subject to frequency limits, certain Colorectal Cancer Screening Tests are payable under the Medicare statute even if the tests would not satisfy the "reasonable and necessary" provision of section § 1862(a)(1)(A). §1861(s)(2)(r); §1861(pp); § 1862(a)(1)(H).

The Balanced Budget Act of 1997, Public Law No. 105-33, § 4104 (1997), established coverage for screening colorectal cancer procedures under Medicare Part B, effective January 1, 1998. Medicare currently covers (1) annual FOBTs, (2) flexible sigmoidoscopy every 4 years, (3) screening colonoscopy for persons at average risk for colorectal cancer every 10 years,[9] or for persons at high risk for colorectal cancer every 2 years, [10] (4) barium enema every 4 years as an alternative to flexible sigmoidoscopy or colonoscopy, and (5) other procedures the Secretary finds appropriate based on consultation with appropriate organizations. Coverage of these screening exams was implemented in regulations through a final rule that was published on October 31, 1997 (Federal Register Notice 10/31/1997, Vol. 62, No. 21, 59079-59082), and was effective January 1, 1998.

Based on consultation with the agency's medical advisors and appropriate organizations, the definition of the term "fecal occult blood test" (FOBT) was defined in 42 CFR section 410.37 of the regulation to mean "a guaiac-based test for peroxidase activity, testing two samples from each of three consecutive stools."

In the Physician Fee Schedule Final Rule for 2003, CMS amended the FOBT screening test regulation definition to provide that it could include either (1) a guaiac-based FOBT, or (2) other tests determined by the Secretary through a national coverage determination (Federal Register Notice 12/31/2002, Vol. 67, No. 251, 79966, 80040).

IV. Timeline of Recent Activities

May 23, 2002	Met with Requestors
January 17, 2003	Request for consideration of Enterix's immunoassay FOBT product accepted by Coverage and Analysis Group. Formal evaluation of this issue began after the effective date of the 2003 Physician Fee Schedule Final Rule.
March 1, 2003	Effective date of change to 42 C.F.R. 410.37
March 3, 2003	

	The CMS 2003 Physician Fee Schedule final rule (CMS-1204-FC) is now effective and the formal evaluation of this NCD has begun. We have referred this issue to the Agency for Healthcare Research & Quality for a technology assessment, which will also include a cost effectiveness analysis for use of this test as a screening test.
August 26, 2003	CMS has received thetechnology assessmentfrom AHRQ. It can be found at http://www.cms.hhs.gov/coverage/download/id87.zip.

V. FDA Approval

Several immunoassay type FOBTs have been approved by the FDA via the 510(k) process with Hemoccult® manufactured by SmithKline Diagnostics, Inc. as the predicate product. These iFOBT approvals include FlexSure® OBT by SmithKline Diagnostics, Inc. in 1996; !nSure™ by Enterix, Inc. in 2001; and Instant-View™ by Alpha Scientific Designs, Inc. in 2002.

VI. General Methodological Principles

When making national coverage determinations concerning the scope of the colorectal cancer screening benefit under Medicare Part B, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that a test is appropriate for general screening in the Medicare population. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the extent to which we are confident that the screening test is appropriate and how it compares to existing covered tests.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s potential risks and benefits.

The methodological principles presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

Methodological strength is a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider).

3. Screening and Characteristics of Screening Tests

Screening refers to the detection of previously undetected disease or conditions through history, physical examination, or testing. Several factors are typically considered such as the burden[11] caused by the disease, the availability of an appropriate screening test, the availability of effective treatments and evidence that early treatment from early detection leads to better health outcomes.[12]

Since screening tests attempt to identify unrecognized disease in asymptomatic individuals and are typically performed on a general population basis, certain characteristics of screening tests should be considered such as:

1. Sensitivity - "the proportion of people with the disease who have a positive test for the disease."[13]
2. Specificity - "the proportion of people without the disease the disease who have a negative test."[14]
3. Simplicity.
4. Cost.
5. Safety.
6. Acceptability.

Ideally, a screening test should have high sensitivity, high specificity, low cost, high safety, and high acceptability to both individuals and clinicians. High sensitivity is desirable since more cases will be identified and in turn fewer cases will be missed. Since positive results are usually further evaluated, high specificity is also desirable so fewer false positive results will be obtained and fewer individuals will be subjected to unnecessary and potentially harmful confirmatory tests and treatments.

In addition, the positive predictive value (PPV) of a screening test is frequently discussed. PPV refers to the probability of having a particular disease if the test result for the disease is positive; and takes into account the prevalence of the disease. In general, the PPV of a screening test is usually low even if the screening test has a high sensitivity and specificity, since prevalence is usually low in the screened population.

Similar to costs, cost effectiveness or cost effectiveness ratios are also commonly considered for screening tests in the preventive medicine community. Cost effectiveness analysis takes into consideration the "net cost of implementing an intervention with the effectiveness of the intervention."[15] Cost effectiveness is operationally defined as the "net cost divided by the net effectiveness."[16] For CRC screening, cost effectiveness analyses have reported results as cost per life saved or cost per cancer averted. A ratio of $50,000 or less per life saved is often accepted by health economists as indicating that the intervention is "cost-effective."

VII. Evidence

A. Introduction:

Colorectal cancer screening using fecal occult blood testing is recommended by a number of prominent professional organizations including the U.S. Preventive Services Task Force, the American Cancer Society and the American Gastroenterological Association. Several randomized controlled trials have demonstrated mortality reductions from screening with guaiac FOBT.[17] Since reduction in mortality has been shown as a primary outcome and both gFOBT and iFOBT detect hemoglobin in the stool, the need for survival data from iFOBT studies may be somewhat lessened: "As Fletcher has pointed out, if new screening tests are truly more accurate than Hemoccult II, their effectiveness need not be confirmed by randomized, controlled trials, since the ability of Hemoccult II to save lives that might have been lost to colorectal cancer has already been shown."[18] Attention may be focused on comparing specific test performance results.

B. Discussion of Evidence:

1. Questions

Is there evidence to conclude that iFOBT is comparable to or better than gFOBT in terms of the characteristics of a screening test?

Is there evidence to conclude that screening with iFOBT improves net health outcomes, such as mortality and quality of life?

2. External Technology Assessment

CMS asked AHRQ (tasked to Erasmus University, Memorial Sloan-Kettering Institute Cancer Center and National Cancer Institute) to conduct a technology assessment on iFOBT to:

- compare iFOBT to gFOBT in terms of cancers detected, cancer deaths averted, and costs;
- assess cost-effectiveness; and
- estimate reimbursement levels of iFOBT at which cost-effectiveness would be equal to gFOBT at current Medicare reimbursement.

This report entitled "A Comparison of the Cost-Effectiveness of Fecal Occult Blood Tests with Different Test Characteristics in the Context of Annual Screening in the Medicare Population" was received in August 2003.[19] The results were generated using a simulation model, MISCAN-COLON, developed by Erasmus University.[20] In this technology assessment, test sensitivities and specificities were varied according to the most likely values from an extensive literature review to predict the outcomes specified above. The TA compared iFOBT (priced at the Enterix-recommended $28.00) to Hemoccult II® and Hemoccult Sensa® at the Medicare reimbursement of $4.50. The model assumed that there were no screenings prior to age 65 years and 100% compliance. The major findings included:

a. Assuming sensitivities of 40%, 70% and 70% for Hemoccult II®, Hemoccult Sensa®, and iFOBT respectively, iFOBT would detect more cancers than Hemoccult II® and a similar number of cancers as Hemoccult Sensa®.
b. All FOBTs were cost-effective. Hemoccult II® at $4.50 had a cost-effectiveness ratio of $1,071 per life year gained and iFOBT at $28.00 had a cost effective ratio of $4,500 per life year saved assuming 100% compliance (lower levels of compliance would increase the cost per life year gained).
c. Compared to Hemoccult II® gFOBT at $4.50, iFOBT would have an equal cost-effectiveness if priced at $13.00 with the more favorable assumption of 98% specificity.[21]

3. Internal Technology Assessment

To compare test characteristics and to evaluate evidence on health outcomes, Medline from 1996 was searched iteratively using the following keywords: fecal blood or FOBT with and without immunoassay or immunochemical. Studies on animal subjects and reports in languages other than English were excluded. There were no recorded studies on the effect of iFOBT screening on net health outcomes such as morbidity and mortality. Three studies that directly compared gFOBT to iFOBT and 2 studies on compliance were identified and are summarized below. Several studies on test characteristics of individual tests have been published but these were not included in our analysis since comparisons across studies were considered in the AHRQ technology assessment.

In 1996, Allison and colleagues reported the results of an observational study to evaluate the sensitivity, specificity, and predictive value of Hemoccult II®, Hemoccult II SENSA®, HemeSelect®, and the combination of Hemoccult II SENSA® and HemeSelect®. There were 8104 participants included. All were sent all three types of tests. Over 90% of the gFOBT cards were completed and over 60% of the iFOBT cards were satisfactorily completed. Colonoscopy was performed in 78% of the patients with positive Hemoccult II®, 36% with positive SENSA®, and 81% with positive HemeSelect®. The authors determined the sensitivity for cancer of Hemoccult II® gFOBT was 37.1% and specificity was 97.7%. The sensitivity for cancer of HemeSelect® iFOBT was 68.8% and specificity was 94.4% (please see Table 1 in Appendix 1). The authors stated: "HemeSelect requires a larger sample and more even spreading of the stool on the collection cards than the guaiac tests and is more expensive to manufacture and develop. There were many more unsatisfactorily prepared HemeSelect cards than cards for the other tests. Nevertheless, HemeSelect's performance characteristics were better than those of Hemoccult II." They concluded that "HemeSelect and a combination test in which HemeSelect is used to confirm positive Hemoccult II Sensa results improve on Hemoccult II in screening patients for colorectal carcinoma."[22] In this study, colonoscopy was not performed on all positive FOBT tests. Univariate and regression analyses were used and 95% confidence intervals were calculated by methods for proportions.

In 1997, Rozen and colleagues reported the results of an observational study to determine various performance characteristics of Hemoccult II®, Hemoccult SENSA®, HemeSelect® and FlexSure®. Of the 403 individuals that completed all 4 tests, 390 (97%) were asymptomatic participants coming to the CRC screening service. Participants with positive FOBT underwent either sigmoidoscopy or colonoscopy. The authors determined the sensitivity for adenomas $\geq$ 1.0 cm or carcinomas of Hemoccult II gFOBT was 62.5% and specificity was 95%. The sensitivity for adenomas $\geq$ 1.0 cm or carcinomas of FlexSure® iFOBT was 62.5% and specificity was 97% (please see Table 2 in Appendix 1). The authors concluded that "guaiac tests were as sensitive as immunochemical tests for clinically significant colorectal neoplasia, but with significantly lower predictive positive values."[23] In this study, endoscopic evaluation was not performed on all participants. Univariate analyses were used and 95% confidence intervals for proportions were calculated.

In 2000, Greenberg and colleagues reported the results of an observational study to evaluate sensitivity and specificity of various fecal occult blood tests (Hemoccult II®, Hemoccult SENSA®, HemeSelect®, FlexSure®, and a combination of SENSA with iFOBT) compared to colonoscopy. A total of 554 patients undergoing elective colonoscopy for specified indications were enrolled. Each patient had all tests performed. Over 90% of tests were completed. The authors determined the sensitivity for cancer of un-rehydrated Hemoccult II gFOBT was 85.7% and specificity was 92.8%. The sensitivity for cancer of FlexSure® iFOBT was 87.5% and specificity was 86.2% (please see Table 3 in Appendix 1). They concluded that "compared to single tests, the combination test with the highly sensitive SENSA and an immunochemical test had slightly reduced sensitivity but significantly fewer false-positive tests than any single test."[24] In this study, all patients were given every test and underwent colonoscopy. Univariate analyses were used and 95% confidence intervals were calculated by methods for proportions.

In 2003, Cole and colleagues reported the results of a randomized study to evaluate the effects on participation in colorectal cancer screening of 3 different fecal occult blood tests: Hemoccult SENSA®, FlexSure®, and !nSure®. Of the 4000 names randomly selected from the Australian Electoral Commission list, 606 individuals were randomly assigned to each group (total n=1818). Invitations for screening along with the specific test kits were sent to the invitees. A follow-up reminder was sent 6 weeks after the initial mailing. At 12 weeks, 142 (23.4%) individuals in the Hemoccult SENSA® group, 185 (30.5%) individuals in the FlexSure® group, and 240 (39.6%) individuals in the !nSure™ group had returned the tests ($p<0.001$). The authors concluded that "the brush-sampling faecal immunochemical test for haemoglobin (!nSure™) achieves the best participation rates by simplifying sampling and removing the need for restrictions of diet and drugs."[25] In this trial, neither the participants nor the clinicians were masked to the test. Univariate and multivariate analyses were performed. There was no control group.

In 2003, Young and colleagues reported the results of an observational study to compare brush-based fecal immunochemical test for hemoglobin to spatula-sampling immunochemical test. 524 individuals scheduled for diagnostic or surveillance colonoscopy consented to participate. Patients were excluded if a sample card was not returned in a specified time. Of the 524 enrolled, 443 completed the full study. The results showed similar sensitivities for cancer between brush-based and spatula tests (75% and 80.5%, respectively); similar sensitivities for adenomas $\geq$ 10 mm between brush-based and spatula tests (41.4% and 44.8%, respectively); and similar specificities between brush-based and spatula tests (97.8% and 97.2%, respectively). The authors concluded that !nSure™ is "as sensitive and specific" as FlexSure® for fecal globin.[26] In this study, 81 patients were excluded. The numbers of exclusions were not reported separately for each group. This would be necessary to calculate compliance.

In 2003, Griffiths and colleagues reported the results of a computerized decision-analysis to evaluate the cost-effectiveness of immunochemical FOBT (!nSure™) versus guaiac FOBTs, colonoscopy, and no screening. Ten hypothetical cohorts of 25,000 persons per cohort, all aged 50 and at average risk for CRC, were entered into a computer simulation model. Base case analyses were performed using "baseline epidemiologic, test performance, cost, and utility inputs." The authors concluded: "The base case results suggest the immunochemical FOBT InSure is a cost effective alternative to guaiac-based FOBTs. Although screening with InSure resulted in higher costs than HII (Hemoccult II®), it resulted in fewer colorectal cancer cases and deaths. Further, InSure resulted in lower costs than HII Sensa, ever though the assumed base case cost of the test itself was $25 per test as compared to $4.49 for HII Sensa, but was equally effective at reducing deaths due to colorectal cancer."[27] In this analysis, the base case analyses assumed 100% participation in screening. Sensitivity analyses were performed at varying degrees of compliance. All tests had projected cost effectiveness less than $30,000 per cancer case prevented.

4. Evidence-based Recommendations

a. U.S. Preventive Services Task Force[28]

- "The USPSTF strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer. An recommendation.
  The USPSTF found fair to good evidence that several screening methods are effective in reducing mortality from colorectal cancer. The USPSTF concluded that the benefits from screening substantially outweigh potential harms, but the quality of evidence, magnitude of benefit, and potential harms vary with each method.

  The USPSTF found good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer."

  "There are insufficient data to determine which strategy is best in terms of the balance of benefits and potential harms or cost-effectiveness. Studies reviewed by the USPSTF indicate that colorectal cancer screening is likely to be cost-effective (less than $30,000 per additional year of life gained) regardless of the strategy chosen."

Only guaiac FOBTs were evaluated. The task force stated: "Other stool tests have been proposed to improve the accuracy of screening for fecal occult blood. Although some newer techniques, including quantitative measures of heme and genetic stool markers, hold promise, they have not been evaluated with respect to mortality reduction (as the Hemoccult® FOBT has been)."[29]

b. Health Canada National Committee on Colorectal Cancer Screening[30]

Screening should be offered to "a target population of adults aged 50 to 74 years of age, using unrehydrated Hemoccult II or equivalent as the entry test."

"Guaiac tests and immunologic assays are those that are suitable for CRC screening. The guaiac tests have been the most widely used and evaluated in FOBT screening trials in the form of the Hemoccult, Hemoccult II while Hemoccult II Sensa has only been evaluated in a few studies. The guaiac-based tests are also the simplest and the least expensive, but delay in processing guaiac-based tests has been shown to decrease sensitivity as a result of dehydration. Test interpretation has also been shown to be highly dependent on the experience of the interpreter."

c. American Cancer Society (ACS)[31]

"Adults at average risk should begin colorectal cancer screening by age 50." The 2001 guidelines provided 5 options:
1. FOBT annually
2. Flexible sigmoidoscopy every 5 years
3. Annual FOBT plus flexible sigmoidoscopy every 5 years
4. DCBE (double-contrast barium enema) every 5 years
5. Colonoscopy every 10 years.

"The most commonly used FOBTs are guaiac-based tests, such as Hemoccult II® and Hemoccult SENSA® (Smith, Kline, and French, Sunnyvale, CA), which are uncomplicated and can be processed in the physician's office. There are immunochemical-based FOBTs that may be processed in a laboratory, or in a doctor's office but they are much less commonly used."

d. American College of Gastroenterology (ACG)[32]

Risk Category	Definition	Age to Start Screening	ACG Recommended Screening	Alternative Strategy
Average	Age 50 or older and no other risk factors	50 years	Colonoscopy every 10 years	Annual fecal occult blood test plus flexible sigmoidoscopy every 5 years

Fecal occult blood test.
"One of the presentations of colon cancer is chronic blood loss in the stool. Sometimes, such blood loss is so minimal, it cannot be seen when the stool is inspected in the toilet. Your doctor will ask you to place a small stool sample on a special card which is returned to the doctor or lab to test for occult (hidden) blood. This test is done annually. If the test is positive, colonoscopy should be done."

e. American Gastroenterological Association (AGA)

"Offer yearly screening with fecal occult blood test (FOBT) using a guaiac-based test with dietary restriction or an immunochemical test without dietary restriction. Two samples from each of 3 consecutive stools should be examined without rehydration. Patients with a positive test on any specimen should be followed up with colonoscopy."[33]

5. Public Comments

CMS has reviewed several comments on iFOBT and the AHRQ technology assessment as follows:

11/21/03 Boyd Buser on behalf of the American Osteopathic Association
Dr. Buser wrote: "It should be noted that the national gastroenterology societies continue to support colonoscopy/sigmoidoscopy as the "gold standard" for screening asymptomatic individuals for colorectal cancers. Given the relative lack of supporting scientific evidence and the high cost of the immunoassay FOBT, we would not recommend that Medicare cover the cost of this test until more evidence accumulates to support the long-term cost/benefit ratio."

01/16/03 Thomas Russell on behalf of the American College of Surgeons
Dr. Russell wrote: "We think it is reasonable to have testing on a much larger scale before adopting the immunoassay FOBT as an alternative to the guaiac FOBT. Ideally there would be long term (lasting at least 10 years) studies of large groups of people." The author also stated: "In short, we believe there should be studies of this test (immunoassay FOBT) to determine its utility in large groups of people in the United States before coverage as a screening test is extended to it. CMS then must evaluate whether the test is cost effective. At present time, we cannot now support a positive coverage determination."

03/28/03 Robert Smith, Ph.D. on behalf of the American Cancer Society
Dr. Smith wrote: "The American Cancer Society is sensitive to the cost constraint issues and has had a long-standing position that cost can be taken into account when determining coverage requirements; however, only if all other aspects are equal. With respect to the immunoassay FOBT, we recognize that the cost may be slightly higher than traditional guaiac-based FOBTs, but feel that the cost of adding this test as an option is justified because it will have fewer false positives, helping avoid the costs associated with unnecessary follow-up tests."

09/05/03 Robert Griffiths, MS, ScD from Health Economics Consulting (under contract to Enterix, Inc.)
Dr. Griffiths provided written comments on the AHRQ Technology Assessment. He wrote that "the present analysis demonstrates that at a cost of $28 per test, and over a reasonable range of test performance parameters, the iFOBT is highly cost-effective compared to both no screening and Hemoccult II."

09/09/03 Neil Schlackman, MD and Robert Bruce from Enterix, Inc.
Dr. Schlackman and Mr. Bruce provided written comments on the AHRQ Technology Assessment. They wrote that "the underlying MISCAN model is a useful tool for evaluating the relative cost-effectiveness of various colorectal cancer screening benefits." They also stated that "the many assumptions incorporated into the model render it unsuitable for determining precise pricing levels." They concluded by stating that the overall "data clearly supports a positive National Coverage Decision for brush-based immunoassay FOBTs with age and frequency limits consistent with those for guaiac FOBTs, and, in conjunction with the relative cost-effectiveness analysis contained in the AHRQ report, a payment level of $28.00."

09/10/03 Graeme Young, MD from Flinders University of South Australia
Dr. Young provided written comments on report to AHRQ TAQ. He concluded:

- "The analysis shows that, whatever the assumption, screening by iFOBT is cost-effective in terms of cost per life year saved.
- While there might be some weaknesses in the assumptions used in the model, it ought to be valuable for making comparisons between the tests.
- In making comparisons though, estimates of iFOBT for sensitivity are not quite high enough for cancer and clearly not high enough for adenomas.
- While the model aims at reaching conclusions for populations, it fails to include relative estimates of compliance with testing, in arriving at the range of threshold payments."

09/11/03 Richard Wender, MD from Jefferson Medical College
Dr. Wender provided written comments on the AHRQ TA. He was concerned by the "tone of the AHRQ report and several specific issues that arise repeatedly throughout the document" such as the use of a threshold payment cost-effectiveness analysis and a "budget neutral" pricing level for iFOBT. He also reported that his family practice center has adopted iFOBT with good success and patient compliance rates that "exceed 60% with minimal intervention."

09/23/03 Quest Diagnostics Incorporated
The company provided written comments on FOBT in general and on the AHRQ TA. They indicated that the company has entered into an agreement with Enterix, Inc. to offer !nSure™ iFOBT as an alternative to Hemoccult SENSA®. They do not offer Hemoccult II® to their customers. Quest also noted benefits of iFOBT such as patient compliance and quality control, and requested "an adequate level of reimbursement to cover the costs of performing the iFOBT test, delivering the test results, and the educational efforts related to increasing patient and physician awareness."

09/30/03 John Doherty from Beckman Coulter, Inc.
Mr. Doherty provided written comments on iFOBT and the AHRQ TA. He wrote: "It is our view that extending coverage with adequate reimbursement to include immunoassay FOBT products for colorectal cancer screening will improve healthcare outcomes by broadening patient screening rates. The basic technology is clinically proven to offer improved specificity over guaiac FOBT products thereby reducing the referral rate for more expensive diagnostic procedures such as sigmoidoscopy and colonoscopy. As we have modeled the economics of immunoassay FOBT, a reimbursement in the range of $21-22 should be sufficient to promote adoption of this test."

VIII. CMS Analysis

As revised by section 522 of the Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act of 2000, Pub. L. No. 106-544 (2000), a National Coverage Determination is defined to be a determination by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Act, but does not include a determination about which code, if any, is assigned to a particular item or service covered under title XVIII, or a determination with respect to the amount of payment for a particular covered item or service. § 1869(f)(1)(B).[34]

In general, an NCD is a national policy statement granting, limiting, or excluding Medicare coverage for a specific medical item or service. Often, an NCD is written in terms of a particular patient population that may receive (or not receive) Medicare reimbursement for a particular item or service. An NCD is binding on all Medicare carriers, fiscal intermediaries (FIs), quality improvement organizations (QIOs), health maintenance organizations (HMOs), competitive medical plans (CMPs), and health care prepayment plans (HCPPs). Before October1,2001, scope of benefit NCDs could be reviewed by administrative law judges (ALJs). 42 C.F.R. § 405.860(a)(2) (2002). Effective October 1, 2001, BIPA expanded the definition of NCDs, and provides that all NCDs shall not be reviewed by ALJs under § 1869(f)(1) of the Act, but may be challenged in certain situations in proceedings filed with the Departmental Appeals Board. Notice of Proposed Rule Making, 67 Fed. Reg. 54534, 54536 (August 22, 2002).

As previously mentioned, the scope of the colorectal cancer screening benefit includes coverage for screening fecal occult blood tests (FOBTs). § 1861(pp)(1)(A). Until recently, screening FOBTs were limited to guaiac-based tests for peroxidase activity. 42 C.F.R.§ 410.37(b)(2) (2002). Under our final rules effective March 1, 2003, however, the Secretary has modified the definition to include "other tests as determined by the Secretary through a national coverage determination." 67 Fed. Reg. 79966, 80040 (December 31, 2002). The Secretary has the authority to approve new screening FOBT found to be "appropriate" after consulting with appropriate organizations. § 1861(pp)(1)(D).

For CRC screening with iFOBT, CMS focused on 2 questions:

1. Is there evidence to conclude that iFOBT is comparable to or better than gFOBT in terms of the characteristics of a screening test?

Several studies have reported test sensitivities and specificities for gFOBT and iFOBT separately. The published sensitivity for cancer of un-rehydrated Hemoccult II® gFOBT ranged from 11.1% to 80.8% and specificity ranged from 96.8% to 98.9%.[35] The published sensitivity for cancer of iFOBT ranged from 62% to 100% and specificity ranged from 86.2% to 97.8%.[36]

In our review, we evaluated 3 observational studies (Allison, Rozen, Greenberg) that directly compared gFOBT to iFOBT. In the report by Allison and colleagues, the sensitivity for cancer of Hemoccult II® gFOBT was 37.1% and specificity was 98.1%. The sensitivity for cancer of iFOBT was 68.8% and specificity was 95.2% (please see Table 1 in Appendix 1).[37]

In the report by Rozen and colleagues, the sensitivity for adenomas $\geq$ 1.0 cm or carcinomas of Hemoccult II gFOBT was 62.5% and specificity was 95%. The sensitivity for sensitivity for adenomas $\geq$ 1.0 cm or carcinomas of FlexSure® iFOBT was 62.5% and specificity was 97% (please see Table 2 in Appendix 1).[38]

In the report by Greenberg and colleagues, the sensitivity for cancer of un-rehydrated Hemoccult II® gFOBT was 85.7% and specificity was 92.8%. The sensitivity for cancer of iFOBT was 87.5% and specificity was 86.2% (please see Table 3 in Appendix 1).[39]

The reported results from these 3 comparisons are consistent. It appears that iFOBT has a higher sensitivity for cancer but a specificity for cancer that is probably lower than gFOBT (Hemoccult II®). Since both tests are noninvasive, stool-based tests, both are relatively simple to perform and safe. The cost of iFOBT ($28 MSRP) is several times higher than gFOBT (Medicare payment of $4.50). At a cost of $13.00, iFOBT would have an equivalent cost-effectiveness ratio compared to gFOBT at $4.50 as reported in the AHRQ technology assessment.[40] Griffiths and colleagues performed separate cost-effectiveness simulations and found similar results: all tests (iFOBT, gFOBT, colonoscopy) had cost per cancer case prevented under $30,000.[41] However, it should be noted that the data on iFOBT are consistently less extensive (fewer studies, smaller sample sizes, and shorter follow-up times) than the data on gFOBT, making the point estimates of sensitivity and specificity somewhat less reliable

On acceptability, Cole and colleagues reported a significantly higher rate of screening among randomly invited participants for iFOBT compared to gFOBT (combined 35% versus 23.4% respectively; please see Table 4 in Appendix 1). The authors postulated that the removal of dietary and drug restrictions with iFOBT was associated with increase in rates over gFOBT and that simplified sampling was associated with an additional increase.[42] However, in this study, it was not possible to mask participants to the type of test they received due to different collection methods, so potential preconceptions about a particular test may have influenced response rates. Nevertheless, it appears reasonable that the removal of dietary and medication restrictions with iFOBT (both FlexSure® and !nSure™) would reduce potential barriers to screening and thus may result in higher response rate compared to gFOBT. It is more difficult to interpret the effect of simplified sampling (brush technique versus spatula) on screening rates since another important difference exists between the two tests: !nSure ™ required sampling from 2 stools while FlexSure® required sampling from 3 stools. It is unclear which factor, simplified sampling or the reduced sampling requirement, has the greater influence on the response rates reported by Cole and colleagues. However, an increase in compliance of up to 50% (combined results; please see Table 4 in Appendix 1) using iFOBT in lieu of gFOBT appears to be a reasonable interpretation of this data.

In addition to the clinical studies, 2 evidence-based practice guidelines and 3 professional association recommendations on colorectal cancer screening were reviewed. The USPSTF did not formally evaluate iFOBT while Health Canada and the AGA stated either gFOBT or iFOBT is suitable for CRC screening. ACS and AGC did not differentiate between types of FOBTs. CMS also received 9 written comments from individuals and/or manufacturers on iFOBT or the AHRQ TA. Of these, 7 were supportive of iFOBT and Medicare coverage of iFOBT. Two believed that additional long-term, population studies on the costs and benefits of iFOBT are needed. While several organizations suggested that iFOBT should be available as a screening option, none interpreted the existing data to suggest that iFOBT should replace gFOBT.

Overall, when considering the characteristics of a screening test, it appears that iFOBT is at least as good as, and may be better in some aspects than, gFOBT. Although the cost of iFOBT is higher than gFOBT, the American Cancer Society believe that "the cost of adding this test as an option is justified."[43] Thus, there is adequate evidence on the ability of immunoassay fecal occult blood test (iFOBT) to function as an appropriate colorectal cancer screening test.

2. Is there evidence to conclude that screening with iFOBT improves net health outcomes, such as mortality and quality of life?

There were no published studies on the improvements of net health outcomes (morbidity and mortality) from CRC screening with iFOBT. Since several trials have demonstrated the reduction in CRC mortality from annual screening using gFOBT, it may be reasonable to indirectly infer that CRC screening with iFOBT would have similar effects on net health outcomes. Specific trials designed to demonstrate reductions in CRC mortality from annual screening with iFOBT would provide more direct evidence, but would take many years to complete.

IX. Conclusions

Although there is no direct evidence on reduction in CRC mortality and iFOBT has been less well studied, there is adequate evidence on the ability of iFOBT to function as an appropriate CRC screening test. When considering the characteristics of screening tests, both iFOBT and gFOBT are sensitive, specific, simple, safe and acceptable. While the unit cost of iFOBT is generally higher than gFOBT, both are considered cost effective compared to other cancer screening tests.

Ultimately, the goals of any CRC screening program or policy are to increase the overall screening rate and thus to reduce CRC mortality. There is still work to be done since the 2 year CRC screening rate with any method was only 32%% in 1999.[44] To promote screening, CMS has initiated educational activities on screening that targets both providers and beneficiaries. With the addition of another option for screening with potential advantages, CMS hopes to further stimulate awareness of the importance of CRC screening and anticipates an increase in the currently low screening rates with FOBT. Other interventions are certainly needed and have been studied. For example, "when testing was ordered by the patient's provider, FOBT completion rates have been reported to be 50% to 70% and can be increased by an average of 14% with the use of a reminder system."[45] It is likely that simple interventions to increase compliance would be highly cost-effective as well.

It would be contrary to the intent of this determination if only shifts between fecal occult blood tests occurred with no concomitant increase in screening but substantial resultant increases in costs. This scenario would not benefit the Medicare population and would not demonstrate prudent use of public health funds. Thus, CMS encourages the preventive medicine community, primary care providers, manufacturers and beneficiaries to collaborate to improve overall CRC screening.

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1 US DHHS Agency for Healthcare Research and Quality, 2003.

2 Walsh and Terdiman, 2003.

3 USPSTF, 2002.

4 USPSTF, ACS, AGC guidelines.

5 Mandel et al., 1993.

6 Rockey, 1999.

7 Ibid.

8 Manufacturer’s product inserts.

9 The coverage for screening colonoscopy was expanded by the Benefits Improvements and Protection Act of 2000 to include beneficiaries at average risk every 10 years, effective January 1, 2002.

10 Individual at high risk for colorectal cancer means an individual with (1) a close relative who has had colorectal cancer or adenomatous polyp; (2) family history of familial adenomatous polyposis; (3) family history of hereditary nonpolyposis colorectal cancer; (4) personal history of adenomatous polyps; (5) personal history of colorectal cancer; or (6) inflammatory bowel disease, including Crohn’s disease and ulcerative colitis.

11 The burden of disease takes into account incidence, prevalence, morbidity and mortality.

12 Fletcher et al., 1996.

13 Ibid.

14 Ibid.

15 Haddix et al., 1996.

16 Ibid.

17 Pignone et al. 2002.

18 Allison, 2001

19 http://www.cms.hhs.gov/coverage/download/id87.zip

20 Loeve et al., 1999.

21 AHRQ, 2003.

22 Allison et al., 1996.

23 Rozen et al., 1997.

24 Greenberg et al., 2000.

25 Cole et al., 2003.

26 Young et al., 2003.

27 Griffiths et al., 2003.

28 USPSTF, 2002.

29 Pignone et al. for the USPSTF, 2002.

30 Health Canada, 2002.

31 American Cancer Society, 2001.

32 ACG website - http://www.acg.gi.org/patientinfo/cc/patcards.htm

33 Winawer et al., 2003

34 If necessary, CMS will address the appropriate payment limits under § 1861(pp)(1)(D) in a separate document.

35 AHRQ TA, 2003.

36 Ibid.

37 Allison et al., 1996.

38 Rozen et al., 1997.

39 Greenberg et al.,

40 AHRQ TA, 2003.

41 Griffiths et al., 2003.

42 Cole et al., 2003.

43 American Cancer Society, 2003.

44 http://www.mrnc.org/crcreport/results_text.asp

45 USPSTF, 2002.

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